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2-AMINOAZOLE DERIVATIVES

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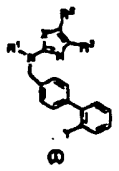
Abstract (Modified)

Objective

A novel 2-aminoazole derivative being an angiotension II receptor antagonist and useful for adjustment of hypertension induced or worsened by angiotensin II and treatment of ischemic cardiac failure, etc., is to be provided. Furthermore, hypotensive drugs containing these compounds are to be provided.

Configuration

A 2-aminoazole derivative represented by the following general formula (I), its pharmaceutically allowable salt, angiotensin II receptor antagonist containing the compound and hypotensive drug.



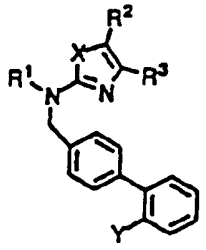
(I)

(In the formula, R^1 is a hydrogen atom, alkyl group, alkenyl group, cycloalkyl group, aryl group, or heteroaryl group; R^2 and R^3 are independently and respectively hydrogen atoms, halogen atoms, alkyl groups which may be substituted; alkenyl groups which may be substituted, cyclic alkyl groups, hydroxycarbonyl groups, etc.; and Y is a hydroxycarbonyl group or heteroaryl group.)

Claims

1. A 2-aminoazole derivative represented by the general formula I or its pharmaceutically allowable salt.

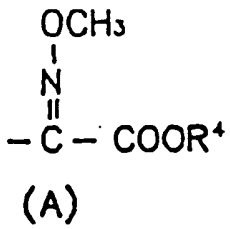
(Structure 1)



(I)

In the formula, R^1 is a hydrogen atom, alkyl group, alkenyl group, cycloalkyl group, aryl group, or heteroaryl group; R^2 and R^3 are independently and respectively hydrogen atoms, halogen atoms, alkyl groups which maybe substituted, alkenyl groups which maybe substituted; cyclic alkyl groups, alkoxy groups, hydroxycarbonyl groups, alkoxycarbonyl groups, amino groups which maybe substituted, acyl groups, aryl groups, heteroaryl groups, or groups represented by the general formula A;

(Structure 2)



(A)

(where R^4 is an alkyl group, alkali metal atom or alkaline earth metal atom); X is S, O or N-R (where R is a hydrogen atom or alkyl group which may be substituted or cyclic alkyl group); and Y is a hydroxycarbonyl group or heteroaryl group.

2. The 2-aminoazole derivative or its pharmaceutically allowable salt of Claim 1 wherein X is an S atom.

3. The 2-aminoazole derivative or its pharmaceutically allowable salt of Claim 1, wherein R^1 is an alkyl group, R^2 is a hydroxycarbonyl or tetrazolyl group, R^3 is an alkyl group, X is an S atom, and Y is a tetrazolyl group.

4. An angiotensin II receptor antagonist characterized by containing the 2-aminoazole derivative or its pharmaceutically allowable salt of Claim 1.

5. A hypotensive drug characterized by containing the 2-aminoazole derivative or its pharmaceutically allowable salt of Claim 1.

Detailed explanation of the invention

[0001]

Industrial application field

This invention pertains to an angiotensin II receptor antagonist. In particular, it pertains to a 2-aminoazole derivative useful for adjustment of hypertension induced or worsened by angiotensin II and treatment of ischemic cardiac failure, etc. This invention also pertains to a hypotensive drug.

[0002]

Prior art

Angiotensin II is a renin-angiotensin system active substance inside the body for controlling blood pressure, body fluid content and electrolyte balance. Angiotensin II causes blood vessel contraction through an angiotensin II receptor on the cell membrane and consequent blood pressure elevation. Therefore, angiotensin is said to be a substance causing hypertension in various mammals. Angiotensin II conversion enzyme inhibitors (ACE inhibitors) in the angiotensin II formation reaction have been developed and are being practically applied.

[0003]

Angiotension II receptor antagonists are also effective as a hypotensive drug or drug for treating hypertension caused by angiotensin II similarly to ACE inhibitors. In addition, the action is powerful, and those adverse effects of ACE inhibitors such as dry coughing, etc., are not observed. Peptide-type angiotensin II analogs such as salarasin [transliteration], etc., have been studied and reported to have a strong angiotensin II receptor antagonistic action. However,

because of antagonistic characteristics, salarasin generally shows a hypertensive action if the hypertension is not caused by angiotensin II. Furthermore such peptide-type antagonists have been reported to show a short action time in the case of non-oral administration and be ineffective in the case of oral administration (M.A. Ondetti and D.W. Cushman, Annual Reports in Medicinal Chemistry, 13, 82-91 (1978)).

[0004]

Studies on non-peptide angiotensin II receptor antagonists have been being carried to solve the problems of those peptide-type angiotensin II receptor antagonists. As a non-peptide angiotensin II receptor antagonist, Japanese Kokai Patent Application Nos. Sho 56[1981]-71073 and Sho 56[1981]-71074 and published European Patent Application Nos. 0324377, 505954 and 0403159 disclose imidazole derivatives. Japanese Kokai Patent Application Nos. Hei 4[1992]-261156, Hei 4[1992]-120072 and Hei 3[1991]-133964 and published European Patent Application Nos. 499415 and 515265 disclose aminoazin derivatives. Japanese Kokai Patent Application No. Hei 3[1991]-143214 discloses aminoquinoline derivatives, and US Patent No. 5,187,168 discloses aminoquinazoline derivatives. These compounds all show effects as an angiotensin II receptor antagonist, and the development of a novel non-peptide angiotensin II receptor antagonist has been desirable.

[0005]

Object of the invention

The object of the invention is to provide a novel 2-aminoazole derivative useful for adjustment of hypertension induced or worsened by angiotensin II and treatment of ischemic cardiac failure, etc. Furthermore, another object of this invention is to provide a hypotensive drug containing such a compound as the one described above.

[0006]

Configuration of the invention

The abbreviations used in this specification are defined as follows.

[0007]

Me: methyl

Et: ethyl

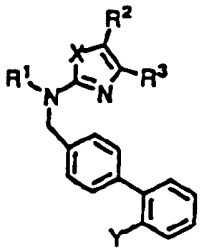
Tr: trityl

Tet: tetrazolyl

(In the case of H-Tet or Tet-H, it is 1H-tetrazol-5-yl, and Tr-Tet shows 2-terityltetrazol-5-yl.)

The 2-aminoazole derivative of this invention is represented by the following general formula I.

[0008]
(Structure 3)

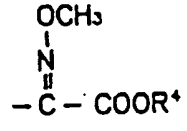


(I)

[0009]

In the formula, R^1 is a hydrogen atom, alkyl group, alkenyl group, cycloalkyl group, aryl group, or heteroaryl group; R^2 and R^3 are independently and respectively hydrogen atoms, halogen atoms, alkyl groups which maybe substituted, alkenyl groups which maybe substituted, cyclic alkyl groups, alkoxy groups, hydroxycarbonyl groups, alkoxycarbonyl groups, amino groups which maybe substituted, acyl groups, aryl groups, heteroaryl groups, or groups represented by the general formula A;

[0010]
(Structure 4)



(A)

[0011]
(where R^4 is an alkyl group, alkali metal atom or alkaline earth metal atom); X is S, O or N-R (where R is a hydrogen atom or alkyl group which may be substituted or cyclic alkyl group); and Y is a hydroxycarbonyl group or heteroaryl group.

[0012]

The above alkyl group for R^1 is a C1-C6 straight or branched chain alkyl group, and specific examples of such an alkyl group are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, sec-butyl, pentyl, hexyl, etc. These alkyl groups may be substituted, and substituents are alkoxy groups and halogen atoms. Specifically, as a substituted alkyl group, there are, for example, alkoxyalkyl groups such as methoxymethyl, ethoxyethyl, etc., and fluoroalkyl groups such as trifluoromethyl, pentafluoroethyl, etc.

[0013]

The above alkenyl group for R^1 is a C2-C7 straight or branched chain alkenyl group, and specific examples include vinyl, allyl, iso-propenyl, pentenyl, etc. These alkenyl groups may be substituted, and substituents are alkoxy groups and halogen atoms.

[0014]

The above cyclic alkyl group for R^1 is a C3-C7 cyclic alkyl group, and specific examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

[0015]

The above aryl group for R^1 is a phenyl group, naphthyl group, etc., which may be substituted, and as a substituent in this case, there are, for example, halogen atoms such as fluorine, chlorine, bromine, etc., and C1-C6 straight or branched chain alkyl or alkoxyl groups. As a specific example of the above heteroaryl group for R^1, there are thienyl, pyridyl, tetrazolyl, thiazolyl, etc.

[0016]

As a specific example of the above halogen atom for R^2 and R^3 in the general formula I, there are fluorine, chlorine, bromine and iodine.

[0017]

The above alkyl groups, which may be substituted for R^2 and R^3, are C1-C6 straight or branched chain alkyl groups similar to the one mentioned above for R^1. These alkyl groups may be substituted with substituents such as halogen atoms, alkoxyl groups, hydroxycarbonyl groups, aryl groups and heteroaryl groups. The halogen atoms and alkoxyl groups of these substituents are the same substituents as those mentioned for the alkyl group of R^1. As an alkoxycarbonyl group of the above substituents, there are those having C1-C6 straight or branched chain alkoxy

groups such as methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc. As an aryl group of the above substituents, there are the same aryl groups as those mentioned for R^1. As a heteroaryl group of the above substituents, there are tetrazolyl, etc.

[0018]

The alkenyl group, which may be substituted for R^2 and R^3, are C2-C7 straight or branched chain alkenyl group similar to those mentioned above for R^1. These alkenyl groups may be substituted with substituents such as halogen atoms, alkoxyl groups, hydroxycarbonyl group, alkoxycarbonyl groups, aryl groups and heteroaryl groups. The halogen atoms, alkoxyl groups, hydroxycarbonyl group, alkoxycarbonyl groups, aryl groups and heteroaryl groups of those substituents are same as those mentioned for the alkyl groups, which may be substituted, of R^2 and R^3.

[0019]

The cyclic alkyl groups for R^2 and R^3 are same as those mentioned above for R^1. The above alkoxyl groups for R^2 and R^3 are methoxy, ethoxy, etc. The above alkoxycarbonyl groups for R^2 and R^3 are those having C1-C6 straight or branched chain alkoxyl groups such as methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.

[0020]

The above amino groups, which may be substituted for R^2 and R^3, are, for example, amino, methylamino, dimethylamino, morpholino, etc. The above acyl groups for R^2 and R^3 are C1-C7 aliphatic acyl groups such as acetyl, propionyl, butylyl, isobutylyl, pentanoyl, hexanoyl, etc. The above aryl and heteroaryl groups for R^2 and R^3 are same as those groups mentioned above for R^1.

[0021]

As an alkyl group for R^4 in the general formula A, there are methyl, ethyl, etc., as an alkali metal, there are sodium, potassium, etc., and as an alkaline earth metal, there are calcium, etc.

[0022]

The above alkyl group, which may be substituted for R in N-R, is a C1-C6 straight or branched chain alkyl group, and specific examples are the same as those alkyl groups mentioned for R^1 described above. These alkyl groups may be substituted with substituents such as alkoxyl, halogen, heteroaryl, hydroxycarbonyl, alkoxycarbonyl, etc. Specific examples of such alkoxyl,

halogen, heteroaryl, hydroxycarbonyl, alkoxycarbonyl, etc., there are those substituents for the alkyl groups, which may be substituted, of R^2 and R^3. The above cyclic alkyl group for R is a C3-C7 cyclic alkyl group, and specific examples are the same cyclic alkyl groups as those mentioned above for R^1.

[0023]

As a heteroaryl group for Y, there is a tetrazolyl group, etc.

[0024]

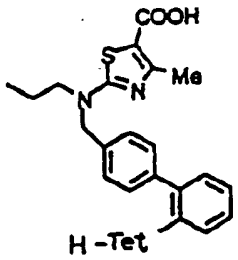
As a pharmaceutically allowable salt of the compound of this invention, there are medically allowable non-toxic salts. For example, there are sodium, potassium, calcium salts, etc. In the specification of this invention, the compound of this invention used below includes a compound (I) as well as its pharmaceutically allowable salt.

[0025]

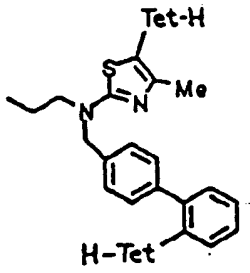
Preferable examples of the 2-aminoazole derivative (I) of this invention are compounds represented by the following formula (I-1), (I-2) or (I-3).

[0026]

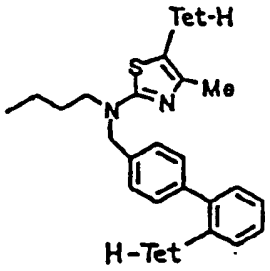
(Structure 5)



(I-1)



(I-2)



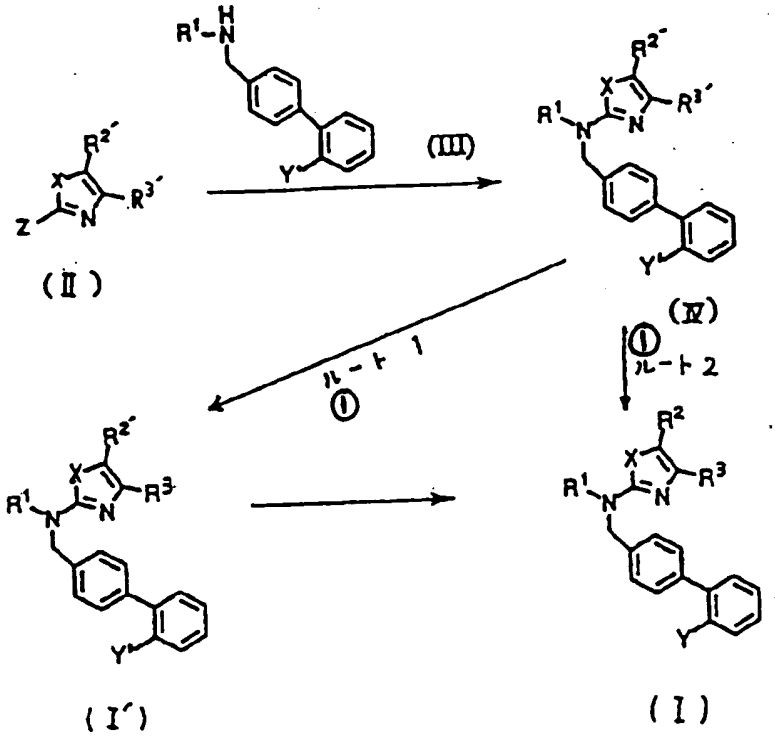
(I-3)

[0027]

The 2-aminoazole derivative of this invention can be prepared by using, for example, the method of (Scheme 1).

[0028]
(Structure 6)

(Scheme 1)



Key: 1 Route

[0029]

In the formulae, R^1, R^2, R^3, X and Y are same as those defined for the Structure (I). Y' is a cyano group, protected tetrazolyl group or protected hydroxycarbonyl group, and it is a group which can be converted to Y by carrying out the reaction. Z is a halogen atom such as chlorine, bromine or iodine, p-toluenesulfonyloxy (tosiloxy) group or methanesulfonyloxy (mesyloxy) group. $R^{2'}$ and $R^{3'}$ are independently and respectively the same groups as those mentioned for R^2 and R^3, groups which can be converted to R^2 or R^3 by carrying out an optional reaction, same groups as those mentioned above for Z or groups selected from cyano group, protected tetrazolyl group, protected hydroxycarbonyl group, etc.

[0030]

As a starting substance (II) in this process, there are compounds such as one with a cyano group for $R^{2'}$, chlorine atom for $R^{3'}$, S for X and chlorine atom for Z, etc. The compound (II) is allowed to react with a biphenylmethyl-substituted amine (III) in the presence of a base such as potassium carbonate, sodium carbonate, sodium hydrogen carbonate, triethylamine, etc., by using a suitable solvent such as acetone, N,N-dimethylformamide, ethanol, etc., to obtain a compound (IV). The substituents $R^{2'}$, $R^{3'}$ and Y' are respectively converted to R^2, R^3 and Y by carrying out optional reactions to obtain a 2-aminoazole derivative (I) of this invention. This method for conversion of substituents is carried out by converting $R^{3'}$ to R^3 and subsequently $R^{2'}$ and Y' to R^2 and Y as shown in Scheme 1 by the route 1 or $R^{2'}$, $R^{3'}$ and Y' simultaneously to R^2, R^3 and Y as shown in Scheme 1 by the route 2, but it is not necessarily limited to these routes.

[0031]

For example, if $R^{3'}$ is a halogen atom, tosiloxy group or mesiloxy group, $R^{2'}$ and Y are cyano, protected tetrazolyl or protected hydroxycarbonyl groups, the compound (IV) is allowed to react with an optional alcohol or amine in the presence of a base such as potassium carbonate, sodium carbonate, sodium hydrogen carbonate, triethylamine, etc., by using a suitable solvent such as acetone, N,N-dimethylformamide, ethanol, etc., according to the route 1 to obtain a compound (I'). The substituent R^3 of (I') prepared in this case, if the reaction of (IV) with an alcohol is carried out, is an alkoxy group corresponding to the alcohol used, and if the reaction of (IV) with an amine is carried out, it is a corresponding amino group. Alternatively, the $R^{3'}$ group of (IV) is converted to a hydrogen atom by carrying out a suitable reduction reaction to obtain a compound (I) where the R^3 group is a hydrogen atom.

[0032]

The substituents $R^{2'}$ and Y' of the compound (I') prepared as described above are converted to desired substituents R^2 and Y, respectively by carrying out optional reactions. For example, if $R^{2'}$ or Y' is a protected tetrazolyl group or protected hydroxycarbonyl group, the protective group is removed by carrying out procedures such as hydrolysis, etc., to obtain a free tetrazolyl group or carboxylic acid. If $R^{2'}$ or Y' is a cyano group, the reaction with an azide compound may be carried out to introduce a tetrazolyl group. As a result it is possible to obtain a 2-aminoazole derivative of this invention where R^2 and Y are independently and respectively hydroxycarbonyl groups or tetrazolyl groups, and R^3 is an alkoxyl group, amino group or hydrogen atom.

[0033]

Alternatively, if the substituent $R^{3'}$ in the compound (IV) is a halogen atom, route 2 may be taken to convert the substituents $R^{2'}$ and Y' of the compound (IV) to the desired substituents R^2 and Y by carrying out optional reactions similar to scheme 1 [sic; probably, route 1] to obtain a 2-aminoazole derivative (I) of this invention where R^3 is a halogen atom.

[0034]

In addition to the above examples of the reactions, any of known optional reactions may be used in combination depending on the desired substituents.

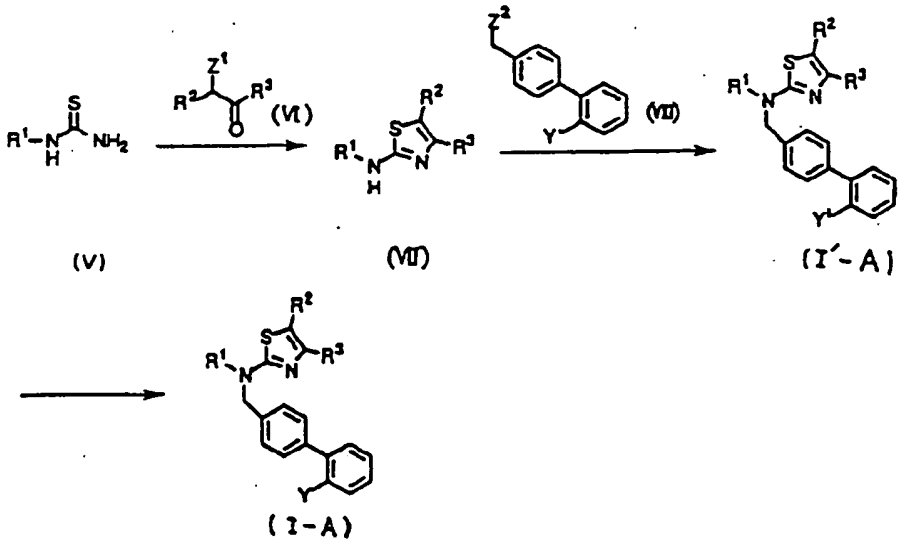
[0035]

The process shown in the following scheme 2 may be used to prepare one specific example of the 2-aminoazole derivative of this invention, that is, 2-aminothiazole derivative having S for X (I-A) in the general formula (I).

[0036]

(Structure 7)

(Scheme 2)



[0037]

In the formulae, R^1, R^2, R^3 and Y are same as those defined for the Structure (I). Y', Z^1 and Z^2 are independently and respectively those groups defined for Z in scheme 1.

[0038]

In this process, an N-substituted thiourea (V) and ketone derivative (VI) are heated at 80-100°C with no solvent or in a suitable solvent such as acetone, ethanol, chloroform, etc., to carry out cyclization and obtain a thiazole derivative (VII). The thiazole derivative (VII) prepared is allowed to react with a biphenyl derivative (VII) [sic; (VIII)] in the presence of a base such as lithium diisopropylamide, lithium bis(trimethylsilyl)amide, etc., at a temperature below room temperature such as a temperature in the range of -78°C to room temperature by using THF as a solvent to obtain a compound (I'-A). The substituent Y' at the 2' position of the biphenyl group (VIII) of this compound (I'-A) prepared is converted to a desired substituent Y by carrying out an optional reaction similarly to the conversion of Y' to Y in scheme 1 to obtain a 2-aminothiazole derivative (I-A) of this invention.

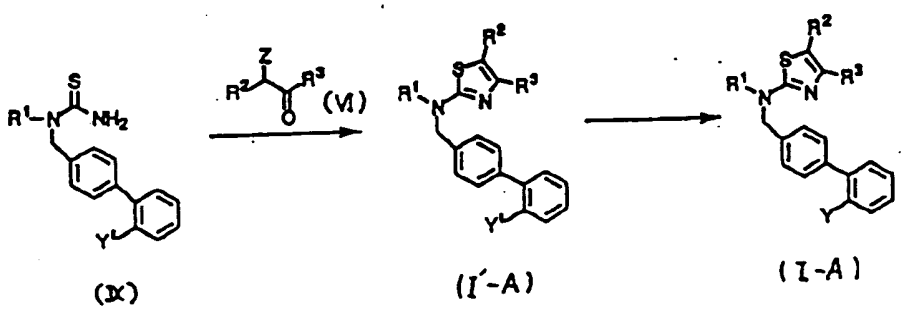
[0039]

The following process shown in the scheme 3 is also usable to prepare a 2-aminothiazole derivative (I-A) of this invention. Especially, if R^2 and/or R^3 is an acyl group or alkoxycarbonylalkyl group, the synthesis by the process shown in the scheme 2 may be difficult, and the process of this scheme 3 is desirably used.

[0040]

(Structure 8)

(Scheme 3)



[0041]

In the formulae, R^1, R^2, R^3, Y and Y' are same as those defined in scheme 2. Z is same as Z defined for scheme 2. In this process, a thiourea derivative (IX) prepared by a known process and ketone derivative (VI) are heated at 80-100°C with no solvent or in a suitable solvent such as

acetone, ethanol, chloroform, etc., to carry out cyclization and obtain a compound (I'-A). The substituent Y' of the compound (I'-A) prepared is converted to a desired substituent Y by carrying out an optional reaction similar to the scheme 2 to obtain a 2-aminothiazole derivative (I-A) of this invention.

[0042]

If R^2 and/or R^3 in the case of an 1-aminothiazole derivative of this invention is a hydrogen atom, halogen atom, alkoxyl group or amino group, the synthesis by the above scheme 2 or 3 may become difficult, and thus, the process of scheme 1 is desirably used.

[0043]

The 2-aminoazole derivative (I) of this invention is usable as an angiotensin II receptor antagonist, especially hypotensive drug and useful for control of hypertension induced or worsened by angiotensin II or treatment of ischemic cardiac failure, etc.

[0044]

The drug composition containing the compound (I) of this invention is administered orally or non-orally. In the case of non-oral administration, there are various methods such as intravenous injection, intramuscular injection, peritoneoclysis, intravenous drip, etc. This drug composition can be administered as a pro-drug. Specific formulations of this drug composition are powder, granules, tablets, capsules, injection formulation, liquid, suspension, emulsion, suppository, etc. In addition to the compound (I) of this invention, the drug formulation of this invention may contain pharmaceutically and pharmacologically allowable suitable excipient, auxiliary, stabilizer, wetting agent, emulsifier and other known additives optionally selected.

[0045]

The dose of the compound (I) of this invention is variable depending on the disease targeted, symptoms, administration subjects, administration methods, etc., but in the case of administration as a drug for treating adult essential hypertension, the oral daily dose is in the range of 1-50 mg, the intravenous injection daily dose is in the range of 1-30 mg, and these doses are preferably administered in 1-3 portions.

[0046]

The effects of the 2-aminoazole derivative (I) of this invention as an angiotensin II receptor antagonist can be evaluated by, for example, the following method. To a mixture of an African green monkey (AGM) kidney-origin COS cell culture with a human angiotensin II

receptor manifested and ^{125}I-labeled angiotensin II, the compounds of this invention is added at various concentrations, and the mixtures are incubated. The concentration (IC_{50}) of the compound of this invention inhibiting 50% of the specific bonding of ^{125}I-labeled angiotensin II is determined from the radioactivity of the ^{125}I-labeled angiotensin II bonded to the culture, and the inhibition constant (Ki) is determined from the following formula.

[0047]
(Equation 1)

$$Ki = (IC_{50}/(1+C/Kd))$$

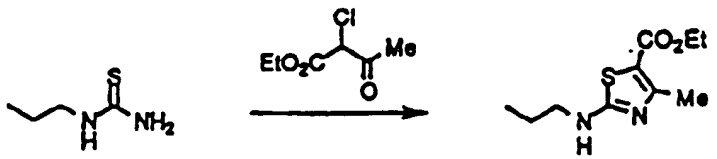
[0048]
In this case, C is the concentration of ^{125}I-labeled angiotensin II, and Kd is the dissociation constant of angiotensin II.

[0049]
As apparent from the results of application examples described later, the 2-aminoazole derivative of this invention shows an excellent angiotensin II receptor antagonistic action.

[0050]
Application examples
This invention is explained based on application and reference examples as follows.

[0051]
Reference Example 1
Production of ethyl 4-methyl-2-(n-propyl)aminothiazol-5-carboxylate (intermediate)

[0052]
(Structure 9)



[0053]
A mixture of N-n-propylthiourea (730 mg, 6.18 mmol) and ethyl 2-chloroacetoacetate (1 g, 6.08 mmol) was heated at 110°C for 15 min, and subsequently, the reaction mixture was partitioned with ethyl acetate and a saturated aqueous solution of sodium hydrogen carbonate.

The aqueous layer was extracted twice with ethyl acetate, the completely organic phase prepared was dried with anhydrous magnesium sulfate, and the solvent was distilled off. The residue obtained was purified by silica gel column chromatography (eluting solvent: ethyl acetate) and furthermore recrystallized from ethyl acetate/n-hexane to obtain 1.2 g of the title compound in a colorless needle crystalline form.

[0054]

Yield: 86.5%, melting point: 103-104°C

Elemental analysis: as $C_{10}H_{16}N_2O_2S$

Calculated (%): C 52.61; H 7.06; N 12.27; S 14.04

Observed (%):C 52.35; H 6.97; N 12.20; S 14.03

NMR ($CDCl_3$) δ:

0.99 (3H, t, J=7.4Hz), 1.33 (3H, t, J=7.2Hz), 1.69 (2H, sext, J=7.4Hz), 2.53 (3H, s), 3.20 (2H, t, J=7.4Hz), 4.26 (2H, q, J=7.4Hz), 6.5-6.8 (1H, broad).

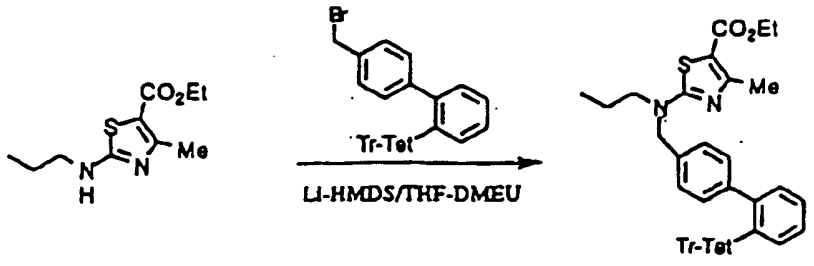
[0055]

Reference Example 2

Production of ethyl 4-methyl-2-[N-(n-propyl)-N-[[2'-(2-trityltetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazol-5-carboxylate (intermediate)

[0056]

(Structure 10)



[0057]

In a solvent mixture of THF (1 mL) and dimethylethyleneurea (0.4 mL), the ethyl 4-methyl-2-(n-propyl)aminothiazol-5-carboxylate (229 mg, 1 mmol) prepared in the Reference Example 1 was dissolved. While cooling over an ice bath, a 1 N THF solution of lithium bistrimethylsilylamide (1.1 mL, 1.1 mol) was added in drops to the above solution, and the mixture was stirred for 20 min. Subsequently, a THF solution (7 mL) of 4-bromomethyl-2'-(2-trityltetrazol-5-yl)biphenyl (665 mg, 1.2 mmol) was added dropwise while cooling over an ice bath. After stirring at room temperature for 20 hr, ice water was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The extract solution obtained was washed with water and a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and subsequently, the solvent was distilled off. The residue obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 30:1) and furthermore recrystallized from n-hexane to obtain 460 mg of the title compound in a white needle crystalline form.

[0058]

Yield: 65.3%; melting point: 71-75°C

Elemental analysis: as $C_{43}H_{40}N_6O_2S$

Calculated (%): C, 73.27; H, 5.72; N, 11.92; S, 4.55

Observed (%): C, 73.18; H, 5.96; N, 11.79; S, 4.49

NMR ($CDCl_3$) δ:

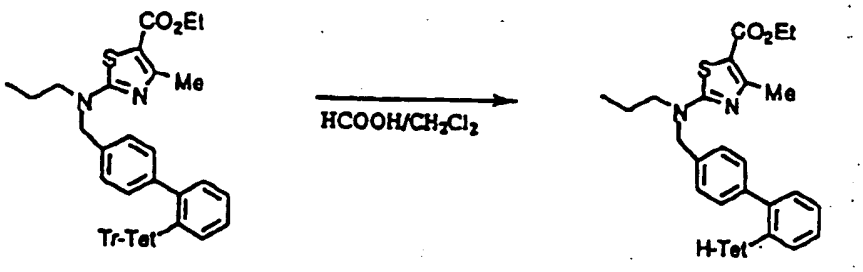
0.85 (3H, t, J=7.0Hz), 1.32 (3H, t, J=7.0Hz), 1.61 (2H, sext, J=7.0Hz), 2.56 (3H, s), 3.19 (2H, t, J=7.0Hz), 4.25 (2H, q, J=7.4Hz), 4.65 (2H, s), 6.

[0059]

Application Example 1

Production of ethyl 4-methyl-2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazol-5-carboxylate (I-4)

[0060]
(Structure 11)



[0061]

To a dichloromethane solution (6 mL) of the ethyl 4-methyl-2-[N-(n-propyl)-N-[[2'-(2-trityltetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazol-5-carboxylate (430 mg, 0.61 mmol) prepared in Reference Example 2, 88% formic acid (8 mL) was added in drops while cooling over an ice bath. After stirring at a room temperature for 4 hr, the reaction solution was concentrated. The residue obtained was dissolved in water, an aqueous solution of sodium hydrogen carbonate was added until it reached neutral pH, and the mixture was extracted 3 times with dichloromethane. The extract solution was dried with anhydrous magnesium sulfate, and the solvent was distilled off. The residue obtained was purified by silica gel column chromatography (dichloromethane:methanol = 30:1) and furthermore freeze-dried by using dioxane to obtain 260 mg of the title compound (I-4) in a white powder form.

[0062]

Yield: 92%
Elemental analysis: as $C_{24}H_{26}N_6O_2S \cdot 0.25H_2O$
Calculated (%): C, 61.72; H, 5.72; N, 17.99; S, 6.87
Observed (%): C, 61.72; H, 5.72; N, 17.87; S, 6.76
NMR ($CDCl_3$) δ: //Insert the NMR data.//

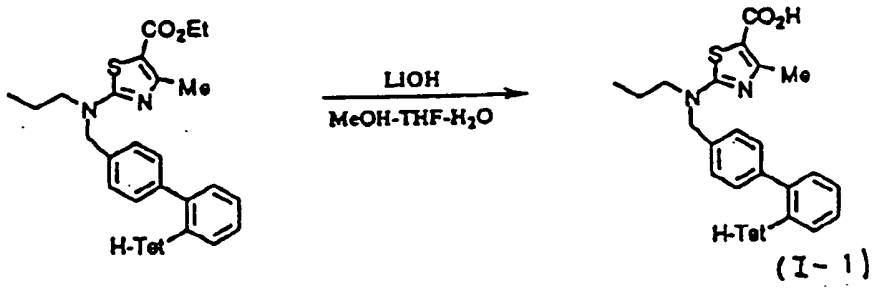
[0063]

Application Example 2

Production of 4-methyl-2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazol-5-carboxylic acid (I-1)

[0064]

(Structure 12)



(I-1)

[0065]

In a solvent mixture of methanol (2 mL), THF (2 mL) and water (0.6 mL), the 4-methyl-2-[n-propyl-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazol-5-carboxylate (260 mg, 0.56 mmol) was dissolved, and lithium hydroxide (120 mg, 5 mmol) was added. After stirring at 70°C for 6 hr by heating, the reaction mixture was concentrated. The residue obtained was dissolved in water, 1 N hydrochloric acid (5.5 mL) was added, and the mixture was extracted 3 times with dichloromethane. The extract solution obtained was dried with anhydrous magnesium sulfate, and the solvent was distilled off. The residue prepared was recrystallized from ether and n-hexane to obtain 140 mg of the title compound (I-1).

[0074]

(I-6) 4-ethyl-2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino] thiazol-5-carboxylic acid

Melting point: amorphous

Elemental analysis: as $C_{23}H_{24}N_6O_2S \cdot 0.5H_2O \cdot 0.5$dioxane

Calculated (%): C, 59.86; H, 5.83; N, 16.75; S, 6.39

Observed (%): C, 59.58; H, 5.83; N, 16.83; S, 6.33

NMR ($CDCl_3$) δ:

0.94 (3H, t, J=7.4Hz), 1.24 (3H, t, J=7.8Hz), 1.69 (2H, sext, J=7.8Hz), 2.97 (2H, q, J=7.4Hz), 3.40 (2H, t, J=7.8Hz), 4.75 (2H, s), 7.14および7.24 (2H×2, ABq, J=8.2Hz), 7.43-7.59 (3H, m), 7.83-7.87 (1H, m)

IR (KBr) cm^{-1}: 1651, 1602。

Key: 1 and

[0075]

(I-7) ethyl 4-trifluoromethyl-2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazol-5-carboxylate

Melting point: amorphous

Elemental analysis: as $C_{24}H_{23}N_6F_3O_2S \cdot 0.2H_2O$

Calculated (%): C, 55.42; H, 4.53; N, 16.16; S, 6.16

Observed (%): C, 55.27; H, 4.62; N, 15.90; S, 6.02

NMR ($CDCl_3$) δ: 0.98 (3H, t, J=7.4Hz), 1.34 (3H, t, J=7.0Hz), 1.73 (2H, sext, J=7.4Hz), 3.46 (2H, t, J=7.4Hz), 4.30 (2H, q, J=7.0Hz), 4.78 (2H, s), 7.20および7.33 (2H×2, ABq, J=8.0Hz), 7.39-7.64 (3H, m), 8.09-8.14 (1H, m)。

Key: 1 and

[0076]

(I-8) 4-trifluoromethyl-2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazol-5-carboxylic acid

Melting point: amorphous

Elemental analysis: as $C_{22}H_{19}N_6F_3O_2S \cdot 0.2H_2O \cdot 0.4$dioxane

Calculated (%): C, 53.75; H, 4.32; N, 15.94; S, 6.08

Observed (%): C, 53.63; H, 4.35; N, 16.17; S, 6.38

NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.4Hz), 1.70 (2H, sext, J=7.4Hz), 3.39 (2H, t, J=7.4Hz), 4.76 (2H, s), 7.14および7.22 (2H×2, ABq, J=8.4Hz), 7.43-7.64 (3H, m), 7.80-7.84(1H, m)

IR (KBr) cm^{-1}: 1690, 1604。

Key: 1 and

[0077]

(I-9) ethyl 4-methyl-2-[N-allyl-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazol-5-carboxylate

Melting point: amorphous

Elemental analysis: as $C_{24}H_{24}N_6O_2S \cdot 0.3H_2O$

Calculated (%): C, 61.86; H, 5.32; N, 18.04; S, 6.88

Observed (%): C, 62.05; H, 5.44; N, 17.88; S, 6.71

NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.0Hz), 2.49 (3H, s), 4.07 (2H, d, J=5.4Hz), 4.24 (2H, q, J=7.0Hz), 4.70 (2H, s), 5.26 (2H, m), 5.81 (1H, m), 6.91 (1H, broad), 7.08-8.08 (8H, m)

IR (KBr) cm^{-1}: 3394, 1691.

[0078]

(I-10) 4-methyl-2-[N-allyl-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazol-5-carboxylic acid

Melting point: 130-131°C

Elemental analysis: as $C_{22}H_{20}N_6O_2S \cdot 0.25acetone \cdot 0.25H_2O$

Calculated (%): C, 60.52; H, 4.91; N, 18.61; S, 7.10

Observed (%): C, 60.42; H, 4.94; N, 18.63; S, 7.07

NMR (DMSOd-6) δ: 2.43 (3H, s), 4.07 (2H, d, J=5.0Hz), 4.70 (2H, s), 5.20 (2H, m), 5.78 (1H, m), 7.08および7.24 (2H×2, ABq, J=8.4Hz), 7.50-7.55 (4H, m), 12.44 (1H, broad)

IR (KBr) cm^{-1}: 3110, 1665.

Key: 1 and

[0079]

(I-11) ethyl 4-methyl-2-[N-cyclopentyl-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazol-5-carboxylate

Melting point: amorphous

Elemental analysis: as $C_{26}H_{28}N_6O_2S \cdot 0.25H_2O \cdot 0.25$dioxane

Calculated (%): C, 62.95; H, 5.97; N, 16.31; S, 6.22

Observed (%): C, 62.84; H, 5.98; N, 16.05; S, 6.11

NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.2Hz), 1.50-1.80 (6H, m), 1.95-2.15 (2H, m), 2.46 (3H, s) 4.24 (2H, q, J=7.2Hz), 4.41-4.58 (1H, m), 4.62 (2H, s), 7.11および7.19 (2H×2, ABq, J=8.2Hz), 7.40-7.64 (3H, m), 8.03-8.10(1H, m)

IR (KBr) cm^{-1}: 2960, 1697, 1513。

Key: 1 and

[0080]

(I-12) 4-methyl-2-[N-cyclopentyl-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazol-5-carboxylic acid

Melting point: amorphous

Elemental analysis: as $C_{24}H_{24}N_6O_2S \cdot 0.1$hexane

Calculated (%): C, 62.98; H, 5.46; N, 17.91; S, 6.83

Observed (%): C, 63.10; H, 5.54; N, 17.78; S, 6.60

NMR ($CDCl_3$) δ: 1.57-1.80 (6H, m), 1.88-2.15 (2H, m), 2.43 (3H, s), 4.32-4.80 (1H, m), 4.62 (2H, s), 7.0-7.12 (4H, m), 7.39-7.60 (3H, m), 7.88-7.92 (1H, m), 10.10-10.70 (1H, broad)

IR (KBr) cm^{-1}: 2958, 1653, 1587。

[0081]

(I-13) ethyl 2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazol-5-carboxylate

Melting point: amorphous

Elemental analysis: as $C_{23}H_{24}N_6O_2S$

Calculated (%): C, 61.59; H, 5.39; N, 18.74; S, 7.15

Observed (%): C, 61.39; H, 5.52; N, 18.60; S, 6.99

NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7.4Hz), 1.34 (3H, t, J=7.2Hz), 1.67 (2H, sext, J=7.4Hz), 3.32 (2H, t, J=7.4Hz), 4.30 (2H, q, J=7.2Hz), 4.65 (2H, s), 6.93および7.02 (2H×2, ABq, J=8.2Hz), 7.32-7.60 (4H, m), 7.91-7.96 (1H, m)

IR (KBr) cm^{-1}: 2956, 1695, 1566。

[0082]

(I-14) 2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazol-5-carboxylic acid

Melting point: amorphous

Elemental analysis: as $C_{21}H_{20}N_6O_2S \cdot 0.12$isopropyl ether$\cdot 0.5H_2O$

Calculated (%): C, 59.31; H, 5.20; N, 19.10; S, 7.29

Observed (%): C, 59.36; H, 5.28; N, 19.09; S, 7.24

NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7.0Hz), 1.61 (2H, sext, J=7.0Hz), 3.26 (2H, t, J=7.0Hz), 4.54 (2H, s), 6.86-6.98 (4H, m), 7.30-7.58 (4H, m), 7.86-7.90 (1H, m)

IR (KBr) cm^{-1}: 2966, 1706, 1604。

[0083]

(I-15) ethyl 4-(4'-methoxycarbonyl)butyl-2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazol-5-carboxylate

Melting point: amorphous

NMR ($CDCl_3$) δ:

0.95 (3H, t, J=7.2Hz), 1.33 (3H, t, J=7.2Hz), 1.50-1.80 (6H, m), 2.32 (2H, t, J=6.6Hz), 2.97 (2H, t, J=6.6Hz), 3.38 (2H, t, J=7.8Hz), 3.54 (3H, s), 4.25 (2H, q, J=7.2Hz), 4.79 (2H, s), 7.11および7.20 (2H×2, ABq, J=8.4Hz), 7.41-7.65 (3H, m), 7.96-8.01 (1H, m)。

[0084]

(I-16) 4-(4'-carboxyl)butyl-2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazol-5-carboxylic acid

Melting point: amorphous

NMR ($CDOD_3$) δ:

0.91 (3H, t, J=7.5Hz), 1.50-1.80 (6H, m), 2.32 (2H, t, J=6.0Hz), 2.97 (2H, t, J=6.2Hz), 3.39 (2H, t, J=7.5Hz), 4.75 (2H, s), 7.09および7.21 (2H×2, ABq, J=8.2Hz), 7.50-7.70 (4H, m)。

[0085]

(I-17) 5-acetyl-2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazole

Melting point: amorphous

NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7.4Hz), 1.71 (2H, sext, J=7.4Hz), 2.38 (3H, s), 2.51 (3H, s), 3.43 (2H, t, J=7.4Hz), 4.75 (2H, s), 7.15および7.23 (2H×2, ABq, J=8.4Hz), 7.41-7.65 (3H, m), 8.01-8.06 (1H, m)。

[0086]

(I-18) ethyl 2-([N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazol-4-yl)methoxyiminoacetate

Melting point: 171-172°C

Elemental analysis: as $C_{25}H_{27}N_7O_3S \cdot 0.2$diethyl ether$\cdot 0.5H_2O$

Calculated (%): C, 58.53; H, 5.71; N, 18.52; S, 6.06

Observed (%): C, 58.84; H, 5.61; N, 18.57; S, 6.01

NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7.4Hz), 1.25 (3H, t, J=7.2Hz), 1.75 (2H, m), 3.66 (2H, t, J=8.0Hz), 3.81 (3H, s), 4.03 (2H, s), 4.29 (2H, q, J=7.2Hz), 6.68 (1H, s), 7.34-7.82 (8H, m), 11.98 (1H, broad)

IR (KBr) cm^{-1}: 3316, 1729。

[0087]

(I-19) sodium 2-([N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]thiazol-4-yl)methoxyiminoacetate

Melting point: amorphous

Elemental analysis: as $C_{23}H_{21}N_7O_3SNa_2 \cdot 0.5$methanol$\cdot 2H_2O$

Calculated (%): C, 49.21; H, 4.75; N, 17.09; S, 5.59

Observed (%): C, 49.11; H, 4.84; N, 16.61; S, 5.96

NMR (DMSOd-6) δ: 0.83 (3H, t, J=7.4Hz), 1.60 (2H, m), 3.39 (2H, t, J=7.4Hz), 3.45 (3H, s), 3.99 (2H, s), 6.55 (1H, s), 7.40-8.02 (8H, m)

IR (KBr) cm^{-1}: 1607.

[0088]

(I-20) ethyl 4-methyl-2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]oxazole-5-carboxylate

Melting point: amorphous

NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.4Hz), 1.34 (3H, t, J=7.0Hz), 1.63 (2H, sext, J=7.4Hz), 2.29 (3H, s), 3.37 (2H, t, J=7.4Hz), 4.29 (2H, q, J=7.0Hz), 4.54 (2H, s), 7.0-7.12 (4H, m), 7.37-7.63 (3H, m), 7.88-7.93 (1H, m).

[0089]

(I-21) 4-methyl-2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]oxazol-5-carboxylic acid

[0090]

(I-22) ethyl 5-methyl-2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]imidazol-5-carboxylate

Melting point: amorphous

Elemental analysis: as $C_{24}H_{27}N_7O_2 \cdot 0.25$dioxane$\cdot 0.5H_2O$

Calculated (%): C, 63.01; H, 6.34; N, 20.57

Observed (%): C, 63.25 ; H, 6.37 ; N, 20.44

NMR ($CDOD_3$) δ: 0.89 (3H, t, J = 7.4Hz), 1.35 (3H, t, J=7.2Hz), 1.60 (2H, sext, J=7.4Hz), 2.41 (3H, s), 3.32 (2H, t, J=7.2Hz), 4.31 (2H, q. J=7.2Hz), 4.67 (2H, s), 7.07-7.15 (4H, m), 7.35-7.62 (4H, m)

IR (KBr) cm^{-1}: 2965, 1700, 1660, 1639.

[0091]

(I-23) 5-methyl-2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]imidazol-5-carboxylic acid

[0092]

(I-24) (E) ethyl 3-(2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]-4-methylthiazol-5-yl)-2-propenoate

Melting point: amorphous

NMR ($CDCl_3$) δ: 0.95 (3H, t, J = 7.4Hz), 1.30 (3H, t, J=7.0Hz), 1.71 (2H, sext, J=7.4Hz), 2.30 (3H, s), 3.39 (2H, t, J=7.2Hz), 4.21 (2H, q. J=7.0Hz), 4.76 (2H, s), 5.66 (1H, d, J=15Hz), 7.15-7.32 (4H, m), 7.38-7.61 (3H, m), 7.72 (1H, d, J=15Hz), 8.08-8.12(1H, m).

[0093]

(I-25) (E) 3-(2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]-4-methylthiazol-5-yl)-2-propenoic acid

Melting point: amorphous

NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.2Hz), 1.60-1.70 (2H, m), 2.27 (3H, s), 3.38 (2H, t, J=7.2Hz), 4.72 (2H, s), 5.59 (1H, d, J=15Hz), 7.0-7.60 (7H, m), 7.75 (1H, d, J=15Hz), 7.90-8.0 (1H, m).

[0094]

(I-26) 4-chloro-2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]-5-(1H-tetrazol-5-yl)thiazole

Melting point: amorphous

Elemental analysis: as $C_{21}H_{19}N_{10}ClS \cdot 0.65$dioxane $\cdot 0.8H_2O$

Calculated (%): C, 51.48; H, 4.72; N, 25.44; S, 5.82

Observed (%): C, 51.46; H, 4.68; N, 25.60; S, 5.91

NMR (CD_3OD) δ: 0.94 (3H, t, J=7.4Hz), 1.69 (2H, sext, J=7.4Hz), 3.46 (2H, t, J=7.4Hz), 4.78 (2H, s), 7.10-7.73 (8H, m).

[0095]

(I-27) 4-methoxy-2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]-5-(1H-tetrazol-5-yl)thiazole

[0096]

(I-28) 4-phenyl-2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino] -5-(1H-tetrazol-5-yl)thiazole

Melting point: amorphous

Elemental analysis: as $C_{27}H_{24}N_{10}S \cdot 0.2$hexane $\cdot 0.4H_2O$

Calculated (%): C, 62.14; H, 5.10; N, 25.70; S, 5.88

Observed (%): C, 62.26; H, 4.92; N, 25.56; S, 5.70

NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7.4Hz), 1.73 (2H, sext, J=7.4Hz), 3.50 (2H, t, J=7.4Hz), 4.82 (2H, s), 7.40-7.72 (13H, m).

[0097]

(I-29) 4-(thiazol-2-yl)-2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino] -5-(1H-tetrazol-5-yl)thiazole

Melting point: amorphous

Elemental analysis: as $C_{24}H_{21}N_{11}S_2 \cdot 0.2H_2O$

Calculated (%): C, 54.26; H, 4.06; N, 29.00; S, 12.07

Observed (%): C, 54.63; H, 4.10; N, 28.73; S, 12.22

NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7.4Hz), 1.80 (2H, sext, J=7.4Hz), 3.61 (2H, t, J=7.4Hz), 4.77 (2H, s), 7.15-7.62 (9H, m), 7.84-7.90 (1H, m), 8.04 (1H, d, J=3.4Hz).

[0098]

(I-30) 2-[N-(n-propyl)-N-[[2'-(1-H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]-5-(1H-tetrazol-5-yl)thiazole

Melting point: amorphous

Elemental analysis: as $C_{21}H_{20}N_{10}S \cdot 0.2$hexane$0.5H_2O$

Calculated (%): C, 56.64; H, 5.09; N, 29.75; S, 6.81

Observed (%): C, 56.49; H, 4.90; N, 29.56; S, 6.61

NMR (CD_3OD) δ: 0.95 (3H, t, J=7.4Hz), 1.72 (2H, sext, J=7.4Hz), 3.50 (2H, t, J=7.4Hz), 4.81 (2H, s), 7.12および7.27 (2H×2, ABq, J=8.4Hz), 7.50-7.72 (4H, m), 7.79 (1H, s)

Application Example 4

Evaluation of inhibitory action of 2-aminoazole derivative on ^{125}I-labeled angiotension II receptor

The human angiotensin II receptor gene was incorporated in a manifestation vector pcDNAI, African green monkey kidney-origin COS cell was transfected, and the cell was cultivated for 2-3 days for angiotension II receptor manifestation. To the cultivated cell, 10^{-6}-10^{-10} M of the compound of this invention was added, or without any addition, and the cell was incubated with 100 pM of ^{125}I-labeled angiotensin II at 25°C for 1 hr. After completing the reaction, the ^{125}I-labeled angiotensin II bonded to the cultivated cell was isolated by using a glass fiber filter, and the radioactivity was measured by using a gamma counter. The specific bonding of ^{125}I-labeled angiotensin II to the cultivated cell was determined by subtracting the non-specific bonding obtainable in a system containing 10^{-6} M of non-radioactive angiotensin II from the total bonding. From the concentration (IC_{50}) of the compound of this invention inhibiting 50% of the specific bonding of ^{125}I-labeled angiotensin II to the cultivated cell, the inhibition constant (Ki) was determined by using the following formula.

[0099]

(Equation 2)

$$Ki=IC_{50}/(1+C/Kd)$$

[0100]

Table 1

①化合物	②Ki (nM)
I-1	6.0
I-2	1.1
I-3	0.87

Key: 1 Compound
2 Ki (nM)

[0101]

In the above formula, C is the concentration of ^{125}I-labeled angiotensin II (100 pM), and Kd is the dissociation constant C1-3 nm of angiotensin II.

[0102]

As described above, the inhibitory action of the 2-aminoazole derivative of this invention is strong, and it can be effectively bonded to an angiotensin II receptor.